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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,875	06/18/2001	Lin-feng Chen	UCAL-234	1891

24353 7590 10/06/2005

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,875	CHEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,19-26,28-31 and 43-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *43-48* is/are allowed.

6)☒ Claim(s) *1,3-10,19-26 and 28-31* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JD

DETAILED ACTION

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 4/20/2005. Therefore, this action is not final.

Receipt is acknowledged of an amendment, filed 7/13/2005, in which claims 11-18, 27 and 32-42 were canceled; and claims 7 and 25 were amended. Currently, claims 1-10, 19-26, 28-31 and 43-48 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 3-10, 19-26 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Claim 1 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The claim recites the method step of "detecting a level of deacetylated RelA". However, it is unclear if the detecting step relates back to the "detectably labeled RelA," which is exposed to the test substance, such that the detection of the label provides information regarding the acetylation status of the RelA. Alternatively, the detectably labeled RelA could be independent of the acetylation status of the protein such as a RelA protein comprising a radioactively labeled amino acid that is unaffected by the acetylation state of the RelA protein.

Thus, the relationship between the detectably labeled RelA and detection of deacetylated RelA is unclear.

Claim 3 is vague and indefinite in that the metes and bounds of the claimed method are unclear. Claim 1 recites the method step of "detecting a level of deacetylated RelA." Claim 3 limits the detecting step to "detecting released detectable label." However, it is not clear that "detecting released detectable label" will *necessarily* result in the determination of the level of deacetylated RelA. The specification teaches the labeling of RelA by culturing cells in the presence of Na-[^{3}H]-acetate (e.g. paragraph [0079]). Because other cellular components (e.g. histones) will incorporate and release the labeled acetate, it is not clear that an agent that causes an increase in the release of a detectable label such as labeled acetate will necessarily correlate with the level of deacetylated RNA. For example, an agent may have a significant effect on histone deacetylation resulting in the release of the detectable label, possibly without a significant change in the acetylation state of RelA (e.g. chromatin remodeling independent of the effects of RelA). Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claim 5 is vague and indefinite in that the metes and bounds of the claimed method are unclear. Claim 1 recites the method step of "detecting a level of deacetylated RelA." Claim 5 limits the detecting step to "detection of export of RelA from the nucleus of the cell, wherein detection of RelA export indicates RelA is deacetylated." However, it is not clear that "detection of export of RelA from the nucleus of the cell" will *necessarily* result in the detection of deacetylated RelA. For example, Karin et al (US Patent No. 6,242,253, cited in a prior action) teach an inhibition of nuclear translocation of RelA in TNF-treated cells as compared to cells by

adding an agent (i.e. mutant IKKα kinase) (see pages 4-5 of the Office action mailed 4/6/2004). The response, filed 7/1/2004, to the Office action mailed 4/6/2004 indicates that Karin et al teaches a method for identifying an agent that modulates NF-κB by detecting the phosphorylated state of IκB-α, and that the phosphorylation/dephosphorylation of IκB-α is an entirely different regulatory pathway than that of deacetylation/acetylation of RelA (e.g. pages 7-8). Thus, different pathways contribute to the cellular localization of RelA. Thus, one would not necessarily know which pathway an agent affects merely by detecting the export of RelA from the nucleus to the cytoplasm. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claim 6 is vague and indefinite in that the metes and bounds of the claimed method are unclear. Claim 1 recites the method step of "detecting a level of deacetylated RelA." Claim 6 limits the detecting step to "detection of an increase in RelA binding to IκBα." However, it is not clear that "detection of an increase in RelA binding to IκBα" will *necessarily* result in the detection of deacetylated RelA. For example, Karin et al (US Patent No. 6,242,253, cited in a prior action) teach an inhibition of nuclear translocation of RelA in TNF-treated cells as compared to cells by adding an agent (i.e. mutant IKKα kinase) (see pages 4-5 of the Office action mailed 4/6/2004). The response, filed 7/1/2004, to the Office action mailed 4/6/2004 indicates that Karin et al teaches a method for identifying an agent that modulates NF-κB by detecting the phosphorylated state of IκB-α, and that the phosphorylation/dephosphorylation of IκB-α is an entirely different regulatory pathway than that of deacetylation/acetylation of RelA (e.g. pages 7-8). Thus, different pathways contribute to the cellular localization of RelA. Thus, one would not necessarily know which pathway an agent affects merely by detecting the export

of RelA from the nucleus to the cytoplasm. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claim 7 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The claim recites the method step of "comparing the level of deacetylated RelA in the sample". However, it is unclear if the detecting step relates back to the "detectably labeled RelA," which is exposed to the test substance, such that the detection of the label provides information regarding the acetylation status of the RelA. Alternatively, the detectably labeled RelA could be independent of the acetylation status of the protein such as a RelA protein comprising a radioactively labeled amino acid that is unaffected by the acetylation state of the RelA protein. Thus, the relationship between the detectably labeled RelA and detection of deacetylated RelA is unclear.

Claim 25 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The claim recites the method step of "detecting the level of deacetylated RelA". However, it is unclear if the detecting step relates back to the "nucleotide sequence encoding RelA operably linked to a detectable label," which is exposed to the test substance, such that the detection of the label provides information regarding the acetylation status of the RelA. Alternatively, the detectably labeled RelA could be independent of the acetylation status of the protein such as a RelA protein comprising an epitope tag that is unaffected by the acetylation state of the RelA protein. Thus, the relationship between the detectably labeled RelA and detection of deacetylated RelA is unclear.

Claims 1, 3-10, 19-26 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a level of deacetylated RelA, wherein RelA is detectably labeled so that deacetylation results in release of the detectable label from RelA, and said detecting of deacetylated RelA is by detecting a decrease in detectably labeled RelA, does not reasonably provide enablement for any other method of detecting a level of deacetylated RelA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to methods of identifying agents that modulate NF-κB activity in the transcription of a gene in a eukaryotic cell. The identification of agents is based upon the acetylation status of RelA, a component of NF-κB. An increase in the level of deacetylated RelA in the presence of a candidate agent as compared to the level of deacetylated RelA in the absence of the agent indicates that the agent inhibits the activity of NF-κB.

Claims 1, 3-6 and 19-24 are drawn to a method comprising the steps of (i) contacting a candidate agent with a eukaryotic cell in vitro, wherein the eukaryotic cell comprises a detectably labeled RelA, and (ii) detecting a level of deacetylated RelA. Claim 3 limits the

detecting step to detecting released detectable label. Claim 5 limits the detecting step to detecting RelA export from the nucleus of the cell. Claim 6 limits the detecting step to detecting an increase in RelA binding to IκBα.

Claims 7-10 and 23-24 are drawn to a method comprising the steps of (i) exposing a sample comprising a detectably labeled RelA to a test substance, (ii) comparing the level of deacetylated RelA in the sample comprising the test substance to the level of deacetylated RelA in a sample without the test substance, and (iii) determining whether the level of deacetylated RelA is greater in the sample exposed to the test substance than a level of deacetylated RelA in the sample without a test substance.

Claims 25-26 and 28-31 are drawn to a method comprising the steps of (i) contacting a candidate agent with a eukaryotic cell in vitro, wherein the eukaryotic cell comprises a recombinant nucleic acid comprising a nucleotide sequence encoding RelA operably linked to a detectable label, and (ii) detecting the level of deacetylated RelA. Thus, the detectable label is a peptide encoded by the nucleic acid. Claim 28 limits the detectable label to a fluorescent polypeptide.

The nature of the invention is complex in that the screen is intended to identify agents that affect the acetylation status of RelA without any prior knowledge of the function of the agent. The claims encompass methods of indirectly determining the acetylation status of RelA by assaying released detectable label, cellular localization of detectably labeled RelA, and increased binding of RelA to IκBα, for example. Given that the regulation of RelA and NF-κB is a complex process involving multiple regulatory pathways (e.g. phosphorylation and ubiquitination) an indirect determination of RelA acetylation/deacetylation cannot be done

without prior knowledge that the compound does not affect alternate pathways of RelA regulation. (See the discussion below).

Breadth of the claims: The claims are broad in that they encompass any method of detecting a level of deacetylated RelA, including direct and indirect detection. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

State of the art: As discussed in the instant specification, NF-κB is a heterodimer of the proteins p50 and RelA (a.k.a. p65), which is kept in an inactive form and sequestered in the cytoplasm by a family of inhibitory proteins termed the IκBs (e.g. pages 1-2). Signaling molecules are capable of triggering the phosphorylation of IκBα, resulting in the release of NF-κB, unmasking of the NF-κB nuclear localization signal, translocation of NF-κB into the nucleus, and activation of transcription of target genes (e.g. page 2). The phosphorylation of IκBα also results in the ubiquitination of the protein and subsequent proteosomal degradation (e.g. page 2). The specification teaches that the active nuclear form of NF-κB is acetylated on the RelA subunit and that the active acetylated form remains in the nucleus until RelA is deacetylated and can interact with IκBα (e.g. paragraph bridging pages 8-9). Further, the specification teaches that *de novo* synthesis of IκBα restores the ability of IκBα to retrieve nuclear NF-κB and return it to the cytoplasm (e.g. paragraph [00134]).

Guidance of the specification and existence of working examples: The specification envisions labeling RelA with a detectable label such as a radioisotope, fluorescent tag, chemiluminescent tag, enzymes, specific binding molecules (e.g. biotin, streptavidin and digoxin), particles (e.g. magnetic particles) (e.g. paragraph [0069]). The specification envisions the use of cell-free assays or cell-based assays.

The specification teaches that cell-free assay methods generally comprise the following steps: (i) contacting a test agent with a sample having an acetylated RelA subunit, and (ii) assaying for a phenomenon associated with deacetylation of RelA in the presence of the agent (e.g. paragraph [0072]). The specification envisions the assay of phenomena such as direct detection of deacetylated and/or acetylated RelA, detection of NF-κB complexes having p50 and RelA, detection of NF-κB binding to DNA, or detection of NF-κB-mediated transcription of a reporter gene having κB enhancer sequences (e.g. paragraph [0072]). The specification states that a decrease in NF-κB binding to κB sequences indicates that the candidate agent has disrupted the NF-κB complex, which "can be a result of deacetylation of RelA by the candidate agent" (e.g. paragraph [0076]). Thus, the disruption of DNA binding could be caused by other types of disruptions that are not related to the acetylation status of RelA. For example, an agent that disrupts the interaction of p50 and RelA may affect the ability of NF-κB to bind DNA. Further, the specification envisions the identification of compounds that affect the binding of NF-κB and IκB. Based upon what is known about the NF-κB signaling pathway, an agent that affects the phosphorylation state of IκB will affect the binding of NF-κB and IκB. Thus, there is a potential for this indirect measure of NF-κB acetylation to measure IκB phosphorylation. Moreover, the specification teaches the labeling of RelA with Na-[^{3}H]-acetate. This label is specific for acetylated RelA. The specification envisions the detection of deacetylated RelA by measurement of released label. If components in the assay other than RelA become acetylated in the assay, this measure is indirect and could reflect changes in the acetylation status of proteins other than RelA. The specification envisions the use of controls in these assays (e.g. paragraphs [0073] and [0076]). However, it is unclear whether the controls can account for the variety of

effects an agent may have on the components of the cell-free assay. A direct measurement of acetylated RelA taught by the instant specification is the labeling of RelA with Na-[^{3}H]-acetate and detection of RelA, wherein the amount of the tritiated acetate directly associated with RelA is measured.

The specification that cell-based assays generally involve contacting a cell that produces NF-κB with a test agent and determining the effect of the candidate agent upon NF-κB via deacetylation of the RelA subunit (e.g. paragraph [0077]). The specification envisions labeling RelA with Na-[^{3}H]-acetate. The specification envisions measuring released Na-[^{3}H]-acetate as a measure of the deacetylation of RelA. However, it is not clear that the release of Na-[^{3}H]-acetate will necessarily be correlated with the deacetylation of RelA rather than the deacetylation of histones, for example. To directly measure the amount of deacetylated RelA, the specification teaches labeling RelA with Na-[^{3}H]-acetate, exposing the cells to the test agent, preparing an extract of the cells, and measuring the amount of radioactivity in the RelA subunit using thin layer chromatography or by immunoprecipitation of RelA (e.g. paragraph [0079]). The specification teaches that RelA may be immunoprecipitated using an anti-RelA antibody or by modifying RelA to include an epitope tag and using an epitope tag antibody to isolate RelA.

The specification envisions the use of labels that label the RelA protein using other labels such as fluorescent tags or enzymes, which are indirect labels of the acetylation status of RelA (e.g. paragraph [0082]). With regard to the use of fluorescently labeled RelA for the detection of deacetylated RelA, the specification envisions contacting the cell with the test agent for a sufficient period of time and determining the relative location of the detectable label in the cell by fluorescence microscopy (e.g. paragraph [0080]). This method can be extended to other

detectable labels by measuring the amount of label in the cell cytoplasm and in isolated nuclei (e.g. paragraph [0080]).

The working examples provide convincing evidence that the RelA subunit NF-κB can become acetylated in response to cellular signaling by molecules such as TNF-α and deacetylated through the action of HDAC3. The working examples teach the measurement of acetylated/deacetylated RelA by culturing cells in the presence or absence of TNF-α, incubating the cells in the presence of Na-[^{3}H]-acetate and cyclohexamide, preparing cell lysates, and immunoprecipitating RelA with an anti-RelA antibody (e.g. paragraph [00120]). The specification teaches the transfection of cells with a nucleic acid encoding T7-RelA and the immunoprecipitation of RelA using an anti-T7 antibody.

Predictability of the art: The affect of candidate agents on the regulation of NF-κB is unpredictable. While the specification describes TNF-α as a regulator of IκB phosphorylation (e.g. paragraph [0004]), the working examples of the instant specification demonstrate that TNF-α is capable of affecting the acetylation state of RelA. Thus, the measurement of NF-κB activity or cellular localization as an indirect measure of RelA deacetylation is unpredictable.

For example, the specification teaches the labeling of RelA with a fluorescent tag, exposing cells to a test agent, and after a suitable period of time measuring the cellular localization (e.g. [0080]). The specification teaches that IL-1 regulates the phosphorylation of IκB. However, Giuliano et al (US Patent No. 6,416,959) teach that NF-KB translocates to the nucleus upon cellular stimulation with IL-1 or TNF (e.g. column 25, lines 51-67; column27, lines 50-57). Further, Giuliano et al teach that an IL-1 antagonist progressively inhibits the translocation induced by IL-1α, resulting in a shift of labeled NF-KB to the cytoplasm (e.g.

column 25, lines 51-67; Figure 17). It is unclear whether there is a change in phosphorylation, change in acetylation or combination of both driving the change in subcellular localization.

Amount of experimentation necessary: Given the lack of guidance in the specification with regard to the accuracy of the indirect measurement of RelA deacetylation, the quantity of experimentation in this area is very large. In screening any candidate agent, one could not rely on the prior art or present specification to teach how the agent affects multiple different pathways associated with NF-KB cellular localization, activity, etc. Thus, for any agent identified in the screen as an agent that increases the level of deacetylated RelA, additional experiments would need to be performed to confirm the result. One would have to conduct experiments to rule out alternative possibilities such as an inhibition of IκBα degradation, and increase in IκBα expression, a change in IκBα phosphorylation, etc. This process would need to be repeated for every agent identified using an indirect measure of acetylation/deacetylation of RelA.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to use the claimed invention. Therefore, claims are not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 102

Claims 1, 4-7, 19-22, 25-26 and 28-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Giuliano et al (US Patent No. 6,416,959; see the entire reference). **This is a new rejection.**

Giuliano et al teach that regulation of transcription of some gene involves activation of a transcription factor in the cytoplasm, resulting in that factor being transported into the nucleus where it can initiate transcription of a particular gene or genes (e.g. paragraph bridging columns 24-25). Giuliano et al teach that NF-KB translocates to the nucleus upon cellular stimulation with IL-1 or TNF (e.g. column 25, lines 51-67; column27, lines 50-57). Giuliano et al teach a cell-based screening system used to detect compounds that inhibit or induce transcription based upon the change in transcription factor distribution. Giuliano et al validate the assay by plating a human cell line in 96 well microtiter plates and titrating IL-1RA, an antagonist to the receptor for IL-1, in the presence of IL-1α and measuring the distribution as the NucCyt difference in NF-κB localization (e.g. column 25, lines 51-67). The IL-1 antagonist progressively inhibited the translocation induced by IL-1α (e.g. column 25, lines 51-67; Figure 17). In this example, NF-κB is detectably labeled with a fluorescein conjugated antibody (e.g. column 25, lines 51-67). Further, Giuliano et al teach host cells transfected with an expression vector encoding a fusion protein of a transcription factor of interest that translocates from the cytoplasm to the nucleus upon activation and a luminescent protein, such as green fluorescent protein or luciferase, for use in the screening assay to identify compounds that modify transcription factor activation in a cell of interest (e.g. paragraph bridging columns 27-28). Giuliano et al teach a nucleic acid (SEQ ID NO: 177) encoding an NF-κB -GFP chimera for analysis in live cells, wherein the GFP is fused to RelA (i.e. NF-κB p65) (e.g. column 81, lines 1-10). Giuliano et al teach that IκB retains NF-κB in the cytoplasm via a direct interaction with the protein and masking of the nuclear localization sequence of NF-κB (e.g. column 80, lines 57-67). Thus, the method of Giuliano et al necessarily detects an increase in RelA binding to IκBα.

According to the instant specification, movement of a detectably labeled RelA into the cytoplasm indicates that the candidate agent has activity in deacetylation of RelA. According to Giuliano et al, the localization of the detectably labeled RelA shifts from nuclear to cytoplasmic in the presence of IL-1RA. Therefore, in view of applicants' own model and the teachings of the Giuliano et al reference, the teachings of Giuliano et al necessarily constitute an observation of an increase in the amount of deacetylated RelA in treated cells relative to untreated cells.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product) (i.e. the human cells of Giuliano et al do not comprise HDAC3, CBP or p300). See *in re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Conclusion

Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 43-48 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
Art Unit 1636

jad

TERRY MCKELVEY
PRIMARY EXAMINER